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High-Dose Rate Intraoperative Radiation Therapy for Pediatric Solid Tumors

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Background. Sixteen pediatric patients with solid tumors received treatment on a protocol designed to test the feasibility and safety of high-dose rate intraoperative radiation therapy (IOHDR) via a remote afterloader.

Patients and Methods. Patients with Ewing's sarcoma (n = 5), rhabdomyosarcoma (n = 3), synovial cell sarcoma (n = 2), Wilms tumor (n = 2), osteosarcoma, immature teratoma, desmoplastic small round cell tumor, and inflammatory fibrosclerosis were included. IOHDR was used in the initial management of nine patients and at the time of recurrence in seven. Indications for treatment included gross residual disease in 5 and suspected microscopic disease in 11. The general sites treated were the abdomen (n = 3), chest-wall/thoracic cavity (n = 7), and pelvis (n = 6). All of the patients received multiagent chemotherapy prior to the IOHDR procedure, and 5 had been previously treated with external beam radiation therapy. Separate from the procedure during which IORT was performed, 9 patients underwent an attempt at resection at the time of their initial presentation. A dose of 1200 cGy was prescribed to a depth of 0.5 cm from the surface of a multichannel tissue-equivalent applicator. Complications ascribedto IOHDR included an abscess, delayed wound healing, and cytopenia. Four patients received supplemental external beam radiation therapy to the IOHDR site. At the time of IOHDR, 3 patients had disseminated disease within the pleural cavity and one had pulmonary metastases.

Results. With a median follow-up of 18 months, the actuarial rates of local control, metastasis-free, and overall survival at 2 years were 61%, 51%, and 54%, respectively. The patterns of failure were local (n = 1), distant (n = 1), and local + distant (n = 1). Two patients are alive with active disease. Nine are alive with no evidence of disease and the remaining 5 are dead from disease (n = 2), other causes (n = 1), or treatment (n = 2).

Conclusions. The potential to improve local control with high doses of radiation should be balanced against the risk of late effects. The ability to confine the dose of radiation to the primary site and decrease the dose to normal tissues makes IOHDR an important adjunct to external beam radiation therapy. IOHDR can be a safe and integral component in the management of pediatric solid tumors. Med. Pediatr. Oncol. 30:34–39, 1998.

Key words: brachytherapy; pediatric tumors; radiation therapy; sarcoma; Ewing sarcoma

INTRODUCTION

Despite substantial improvement in survival rates due to the success of combined modality therapy, local control remains an important problem in the treatment of pediatric solid tumors. Investigators are reluctant to rely on external beam radiation therapy to solve this problem because of the late effects that are attributable to this modality. Indeed, with the advent of more effective chemotherapy and aggressive surgical approaches, investigators have attempted to limit the role of external beam radiation therapy or its use in terms of dose and volume.

Under certain conditions brachytherapy can be an excellent alternative to external beam radiation therapy. It has inherent tissue sparing properties and dosimetric advantages that can be used to deliver radiation therapy in a conformal and localized manner. Temporary implants, the most commonly employed form of brachytherapy for pediatric patients, are readily performed at most head and neck, truncal, extremity, and intracavitary sites. Catheters or other guiding devices are placed at the time of surgery and loaded with active sources a few days after the operation. These sources dwell for a prescribed time interval and are then removed together with the catheters or device.

The dose-volume advantages of brachytherapy are further enhanced when the treatment is delivered at the time of surgery using a remote afterloader with a high-dose rate source. Normal tissues and radiosensitive organs can be positioned away from the target or shielded while the treatment is delivered. Further, such a method allows for access to intrathoracic, intraabdominal, and pelvic sites which would otherwise require treatment with external beam radiation therapy alone. High-dose

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TABLE I. Clinical and Treatment Characteristics of IOHDR Patients

Patients	8 male, 8 female	Mean age, 13 yrs (range, 5–24)
Extent of disease	Pulmonary metastasis n = 1	Pleural involvement n = 3
Sequencing of IOHDR	Initial management n = 9	Recurrent disease n = 7
Indications for IOHDR	Microscopic disease n = 11	Gross disease n = 5
Additional treatment	Prior to IOHDR	Following IOHDR
Biopsy	n = 16	
Resection	n = 9	
External beam irradiation	n = 5	n = 4
Chemotherapy	n = 16	n = 11
IOHDR procedure		
Dose	1200 cGy n = 13	n = 2 < 1200 cGy < n = 1
Applicators	Single n = 11	Multiple n = 5
Target dimensions	99 cm^2 (range 6–345 cm^2)	
Application time	39 min (range 7–158 min)	

rate intraoperative radiation therapy (IOHDR) is a relatively new modality available to the pediatric patient. It has the potential to serve as a substitute or adjunct to external beam radiation therapy in a manner analogous to conventional brachytherapy.

There are several methods that define IOHDR. Aside from treatment with a high-dose rate remote afterloader in a manner analogous to brachytherapy, IOHDR can be performed using a linear accelerator. The two methods can be compared and contrasted in terms of availability (logistics), treatment time, and access to the target site. The major difference between the two is that IOHDR with a remote afterloader uses a radioactive source that is mechanically transported by the afterloader system to reside interstitially or in a surface-placed applicator. The linear accelerator-based method uses electrons generated by the linear accelerator and the patient must be positioned en face to the accelerator treatment head. The remote afterloader system has geometric advantages in the pediatric patient because the applicators are customized to conform to the target and can be used to treat sites potentially inaccessible to the accelerator gantry.

We have tested the feasibility and safety of high-dose rate intraoperative radiation therapy via a remote afterloader in the treatment of newly diagnosed and recurrent pediatric solid tumors. Sixteen pediatric patients have been treated with IOHDR and form the basis for this report.

MATERIALS AND METHODS

Patients

Sixteen pediatric patients with solid tumors were treated on a protocol designed to test the feasibility and safety of high dose rate intraoperative radiation therapy via a remote afterloader. The protocol was approved by the institutional review board and consent for IOHDR was obtained in all cases. The patients were treated between February 1993 and March 1996. Pertinent clinical and treatment-related information is presented in Table 1. This information is subdivided to include treatment delivered before and after IOHDR in addition to details related to the procedure itself.

IOHDR

IOHDR was administered to all patients during a planned surgical procedure at which time the primary or recurrent tumor was resected in part or totally. IOHDR was administered if microscopic or gross residual disease was suspected or if the site was deemed to be at high risk for recurrence.

We used an applicator system designed at our institution [1,2]. The applicator is composed of a flexible slab of ''tissue-equivalent'' material 1 cm thick. An array of source-guiding catheters are situated 1 cm apart in the central plane of the slab such that the distance from the source to either surface is 5 mm. The length of the slab measured 20 cm and the width was customized at the time of the procedure either by selecting an existing applicator with the required number of catheters or by dividing a larger applicator to achieve the appropriate size.

The area to be treated was outlined jointly by the surgeon and radiation oncologist. The applicator was positioned and the number of catheters and source positions were chosen to ensure coverage of the target. The dose was prescribed at a distance of 1 cm from the source or 5 mm from the applicator surface. When required, lead shielding of normal or critical structures was performed. During the treatment the source (Ir-192) was positioned at 1-cm intervals along the length of the catheters. The dwell time (the amount of time that the source was located at any location within the catheter) of the source was determined by an atlas of dosimetry created uniquely

for that purpose. Details concerning the GAMMAMED afterloader,[1] treatment technique, applicator, and dosimetry have been reviewed elsewhere [1,2]. The patients were remotely monitored during the treatment which was carried out in a shielded operating suite.

Date Analysis

Progression and survival were measured from the date of IOHDR. Actuarial rates of local control, distant control, progression-free, and overall survival were determined using Kaplan-Meier methodology [3]. The median follow-up after IOHDR was 18 months.

RESULTS

Clinical Characteristics

The study included 16 pediatric patients evenly divided between male and female. The average age was 13 years (range, 5–24 years). The histologies included Ewing's sarcoma (n = 5), rhabdomyosarcoma (n = 3), synovial cell sarcoma (n = 2), Wilm's tumor (n = 2), osteosarcoma, immature teratoma, desmoplastic small round cell tumor, and inflammatory fibrosclerosis. At the time of IOHDR, 2 of the patients with Ewing's sarcoma and one with synovial cell sarcoma had pleural space involvement. One patient with Wilm's tumor had pulmonary metastases in the setting of prior whole-lung irradiation.

Pre- and Post-IOHDR Therapy and Indications for Treatment

Fifteen of the patients were treated with cytotoxic chemotherapy and 1 received high-dose corticosteroids prior to radiation therapy. All patients had prior histologic confirmation of their tumors prior to IOHDR. Separate from the procedure during which IOHDR was performed, 9 underwent a major attempt at resection at the time of initial presentation. Five patients had previous external beam radiation therapy with total doses ranging from 2040 to 5400 cGy. Following IOHDR, 11 of the patients received additional chemotherapy. Four of the 11 received high-dose chemotherapy that required an autologous bone marrow rescue. Four patients received supplemental external beam radiation therapy. The sequencing of surgery, radiation therapy, and chemotherapy is presented in Table III, along with clinical and treatment-related details and the disease status of each patient at the time of analysis.

IOHDR Procedures

The chest wall/thoracic cavity was the IOHDR site in 7 patients. Other sites included the pelvis (n = 6) and abdomen (n = 3). The average target dimension was 99 cm^2 (6–345 cm^2). A single applicator was used in 11 patients. Two applicators were required in 2 patients, and three applicators were used in a single patient. The IOHDR prescription dose for the protocol specified 1200 cGy. Thirteen patients received 1200 cGy, one patient received 1500 cGy, and 2 patients received less than 1200 cGy. Clinical and treatment-related characteristics are included in Table 1.

Outcome: Complications

There were 3 complications ascribed to the 16 patients treated with IOHDR. One patient had a pelvic abscess, 1 had delayed wound healing, and 1 had persistent cytopenia following IOHDR. In addition, 1 patient developed changes on CT scan consistent with fluid loculations. This finding was physiologically inconsequential to the patient.

Outcome: Local Control, Disease-Free, and Overall Survival

With a median follow-up time after IOHDR of 18 months (range, 2–39 months), 1 patient with localized disease at time of treatment suffered a local failure, 1 with localized disease at presentation suffered synchronous local and distant failure, and 1 experienced distant failure only. At the time of analysis, 9 patients were alive with no evidence of disease, 2 were alive with disease (1 local failure and 1 with lung metastases at time of IOHDR), and the remaining 5 were dead. Two died of disease (one with local and distant failure and one with distant failure alone), one died of other causes (drowning), and the remaining 2 suffered treatment related deaths (1 in whom cytopenia was ascribed to IOHDR and 1 with pleural space involvement at the time of treatment). Two of the 3 patients with pleural space involvement were alive and without evidence of disease at the time of analysis. These data are summarized in Table II.

DISCUSSION

Assessment of Complications in Pretreated Patients

Evaluation of a new treatment modality requires an understanding of the known complications from other therapies that may be included in a patient's total treatment regimen. This study comprises the results of patients treated extensively before and following a major surgical procedure and IOHDR; it also includes exclusively operative sites prone to postoperative complications (i.e., thoracic cavity, abdomen, and pelvis). All patients had prior chemotherapy. Five patients had radiation therapy, and 9 had major resections before procedures during which IOHDR was performed. In addition, 4 of the 11 patients who received postoperative chemotherapy required a bone marrow transplantation at the

[1]Gamma-Med Iii and 12i, BARKER+, Towaco, New Jersey.

TABLE II. Complications, Patterns of Failure, and Outcome for 16 IOHDR Patients

Complications	
Abscess	n = 1
Delayed wound healing	n = 1
Cytopenia	n = 1
Patterns of Failure	
Local	n = 1
Distant	n = 1
Local + distant	n = 1
Disease Status	
No evidence of disease	n = 9
Alive with disease	n = 2
Dead of disease	n = 2
Dead of other causes	n = 1
Treatment related death	n = 2
Outcome (actuarial at 2 years)	median, follow-up at 18 months range, follow-up at 2–39 months
Local control	61%
Distant control	76%
Progression-free survival	51%
Overall survival	54%

end of high-dose chemotherapy. Four received additional radiation therapy.

If all the complications ascribed to IOHDR were verified, the complication rate would be 19%. The patient with delayed wound healing underwent resection of a synovial cell sarcoma of the ischiorectal fossa after receiving intensive alkylator-based chemotherapy (cyclophosphamide, doxorubicin, vincristine, ifosfamide, and etoposide). Following surgery and IOHDR, the patient received external beam radiation therapy and additional chemotherapy with the same agents. The delayed healing was predictable for such a site after preoperative chemotherapy and resection.

One patient experienced an abscess at the IOHDR site. This patient, with immature teratoma of the presacral region, was previously treated with a subtotal resection and suffered a similar complication. She recurred a second time and was treated with chemotherapy followed by resection and IOHDR. The abscess that occurred following the second resection and IOHDR delayed the timely delivery of postoperative external beam radiation therapy and limited the total dose to 2520 cGy. She was the only patient who recurred locally and is alive with active disease at the primary site receiving further therapy.

The patient with possible IOHDR-related cytopenia was treated for desmoplastic small cell tumor of the mediastinum. The IOHDR site measured 91 cm^2 in the mediastinum. It covered multiple vertebral bodies and approximated the great vessels. The patient also was treated before and after IOHDR with intensive alkylator-based chemotherapy and died of pulmonary fungemia presumably due to refractory cytopenia. The cytopenia was seen only after the procedure during which IOHDR was performed.

Large-Dose, Single-Fraction Treatment as a Substitute or Adjunct to External Beam Irradiation

The radiobiology and use of high-dose single-fraction radiation therapy as a substitute or adjunct to fractionated external beam radiation therapy is under investigation. Determining the dose equivalence for high dose-rate IOHDR, low dose-rate brachytherapy, and fractionated external beam radiation therapy is difficult. Dose equivalence depends on assumptions related to dose rate and overall treatment time in addition to the total dose delivered. It also depends on whether one is attempting to describe tumoral effects or normal tissue tolerance. Models are available to estimate dose equivalence; however, none to date includes other important parameters such as tumor sensitivity, normal tissue tolerance, and the patient's prior therapy [4]. The late effects of radiation therapy depend primarily on fraction size; the early (acute or tumoral) effects depend on fraction size and overall treatment time. The volume sparing advantage of IOHDR is probably reduced if one considers the expected increase in both early and late toxicity which is characteristic of high-dose single fraction treatment. The results of a prospective randomized trial of two different brachytherapy dose rates for patients with cervical cancer confirmed an increased frequency of late effects in patients treated with the higher dose rate [5].

Two of the patients had local failure alone or as a component of failure. The first patient, with immature teratoma of the presacral region, described above, experienced a postoperative complication which delayed the delivery and ultimately resulted in a reduction in the total dose that was delivered to the primary site. The total fractionated dose of 2520 cGy combined with 1200 cGy from the single fraction of IOHDR was insufficient to achieve local control. The second patient, with locally recurrent Ewing's sarcoma of the chest wall after complete resection and chemotherapy, was treated for recurrence with a similar resection, IOHDR, and high-dose chemotherapy in conjunction with total-body irradiation (TBI) to 1500 cGy. The total fractionated TBI dose of 1500 cGy combined with 1200 cGy IOHDR was insufficient to achieve local control. Both patients may have avoided local failure with higher doses of external beam radiation therapy.

Prospective Evaluation of IOHDR for Pediatric Solid Tumor Treatment

Since the assessment of a new modality such as IOHDR is confounded by the heterogeneity of the treated cases, their locally advanced or recurrent presentations, and history of additional treatment, the value of IOHDR in the treatment of pediatric solid tumors rests on phase I (toxicity/dose-escalation) and phase II studies where

TABLE III. Sequencing and Treatment-Related Information by Patient

Age/ sex	Treatment sequence	Histologic diagnosis	IOHDR			Comp	EBRT dose	Chemotherapy agents	Progression		Disease status
			EOD	Site	Dose				Local	Distant	
11/M	BX-CT-STR-IOHDR	ESFT	LA	CW	1200	None		VAdrC/IE	0	0	NED
15/M	BX-CT-GTR-IOHDR-CT-RT	ESFT		CW	1200	Fluid	4500	VAdrC/IE	0	0	NED
19/M	BX-CT-GTR-CT-E-GTR-IOHDR-TBI/ BMT-CT-E	ESFT		RP	1200	None	1500	VAdrC/IE/ BMT(Me)	1	1	DOD
24/M	STR-CT-RT-CT-E-STR-IOHDR-CT-RT	ESFT	LA	CW	1200	None	5580	VAdrC/IE	0	0	NED
6/M	BX-CT-GTR-IOHDR-CT	ESFT		CW	1200	None		VAdrC/IE	0	0	NED
17/F	STR-E-STR-IOHDR	INF/FIB		Pelvis	800	None		Prednisone	0	0	NED
21/F	BX-CT-STR-IOHDR	OS		Sacrum	1500	None		CDDP/Adr/I/ MTX	0	0	DOC
18/F	BX-CT-RT-E-GTR-IOHDR-CT	RMS		Pelvis	1200	None	5400	VACAdr/IE	0	0	NED
20/M	BX-CT-RT-GTR-IOHDR-BMT-E	RMS		RP	1200	None	5400	VACAdr/ BMT(MeE)	0	1	DOD
5/M	BX-CT-GTR-IOHDR	RMS		Pelvis	1200	None		VAC	0	0	NED
14/F	BX-CT-GTR-IOHDR-CT	SYN CELL	LA	CW	1200	None		VAdrC/IE	0	0	TRD
18/M	BX-CT-GTR-IOHDR-RT-BMT	SYN CELL		Pelvis	1000	Healing	5040	VAdrC/ IE-BMT(MeE)	0	0	NED
20/F	STR-CT-GTR-IOHDR-CT-E	DSRCT		MED	1200	Cytopenia		VadrC	0	0	TRD
9/F	STR-CT-E-BX-CT-E-CT-GTR-IOHDR-RT-BMT-E	Teratoma		Pelvis	1200	Abscess	2520	See below[a]	1	0	AWD
10/F	DX-CT-GTR-E-STR-CT-RT-E-GTR-IOHDR	Wilm's-FH		Abdomen	1200	None	3120	VACAdr/IE	0	0	NED
6/F	BX-CT-GTR--CT-E-CT-E-GTR-RT-CT-E-IOHDR-CT-E	Wilm's-FH	DM	Abdomen	1200	None	3000	See below[b]	0	0	AWD

EOD = extent of disease; COMP = complication; BX = biopsy; CT = chemotherapy; STR = subtotal resection; IOHDR = high-dose rate intraoperative radiation therapy; NED = no evidence of disease; ESFT = Ewing's sarcoma family of tumors; LA = locally advanced disease (pleural involvement); CW = chest wall; VadrC = vincristine, doxorubicin, cyclophosphamide; IE = ifosfamide, etoposide; AWD = alive with disease; GTR = gross total resection; FLUID = fluid loculations; E = event (progression of disease); TBI = total body irradiation; RP = retroperitoneum; BMT = bone marrow transplant; Me = melphalan; DOD = dead of disease; INF/FIB = inflammatory fibrosclerosis; OS = osteosarcoma; CDDP = cisplatin; MTX = methotrexate; DOC = dead of other causes; RMS = rhabdomyosarcoma; VACAdr = Actinomycin-D+VAdrC; MeE = melphalan, etoposide; TRD = treatment-related death; SYN CELL = synovial cell sarcoma; DSRCT = desmoplastic small round cell tumor; MED = mediastinum; DX = clinical diagnosis; FH = favorable histology; DM = distant metastases.
[a]cyclophosphamide, carboplatin, etoposide (CCE)/CCE/BMT(IE).
[b]VA, epirubicin/VAdrI/E/CCE/CDDP,AdrE.

IOHDR is used as an adjunct to existing external beam dose and volume standards. Another important issue related to the use of IOHDR in conjunction with external beam irradiation is sequencing. This would also have to be addressed in a protocol setting.

Brachytherapy has been included in some pediatric cooperative group protocols [6]; however, to date there are no prospective data to define its role. At St. Jude Children's Research Hospital, low-dose rate brachytherapy has been used alone or in combination with external beam radiation therapy for patients with non-CNS malignancies [7]. In their series, 43 of 50 patients receiving brachytherapy were disease-free with a median follow-up of 41 months. Fractionated high dose-rate brachytherapy was used alone in the primary treatment of 11 patients with RMS and non-RMS soft tissue sarcoma [8]. In their study, catheters were implanted at the time of surgery and left in place for 8 to 14 days. Fractions of 3 Gy were delivered twice a day to a total dose of 36 Gy. The median disease-free survival was 41 months. Similarly, the Institut Gustave Roussy has employed brachytherapy for the conservative treatment of children with vulvar and vaginal rhabdomyosarcoma and other pediatric malignancies [9,10].

CONCLUSION

IOHDR and conventional brachytherapy have similar problems surrounding their availability and application in the management of the pediatric cancer patient. Few centers combined the expertise of pediatric solid tumor management with brachytherapy or high-dose rate treatment which makes their inclusion in cooperative group protocols unlikely.

At the present time IOHDR has an immediate value for patients with recurrent disease in the setting of previous radiation therapy. Its use in patients destined to receive external beam radiation therapy should be carefully evaluated and subjected to the scrutiny of a protocol. Pediatric patients have most to gain through the advancement of IOHDR. They are the group most likely to benefit from a reduction in the volume of normal tissues treated since their potential for cure often exceeds that of adults.

REFERENCES

1. Harrison LB, Enker WE, Anderson LL: High-dose-rate intraoperative radiation therapy for colorectal cancer, Part 1. Oncology 9:679–683, 1995.
2. Harrison LB, Enker WE, Anderson LL: High-dose-rate intraoperative radiation therapy for colorectal cancer. Part 2, ''Technical Aspects of Brachytherapy/Remote Afterloader.'' Oncology 9: 737–740, 1995.
3. Kaplan ES, Meier P: Non-parametric estimations from incomplete observations. Am Stat Assoc J 53:457–482, 1958.
4. Fowler JF: The linear-quadratic formula and progress in fractionated radiotherapy. Br J Radiol 62:679–694, 1989.
5. Haie-Meder C, Kramer A, Lambin P, Lancar R, Scalliet P, Bouzy J, Gerbaulet A: Analysis of complications in a prospective randomized trial comparing two brachytherapy low dose rates in cervical carcinoma. Int J Radiat Oncol Biol Phys 29:953–960, 1994.
6. Potter R, Knocke TH, Kovacs G, Schmilowski GM, Haverkamp U, Hawliczek R, Seitz W, Rube C, Wuisman P, Maragakis G, et al.: Brachytherapy in the combined modality treatment of pediatric malignancies. Principles and preliminary experience with treatment of soft tissue sarcoma (recurrence) and Ewing's sarcoma. Klinische Padiatrie 207:164–173, 1995.
7. Fontanesi J, Rao BN, Fleming ID, Bowman LC, Pratt CB, Furman WL, Coffey DH, Kun LE: Pediatric brachytherapy. The St. Jude Children's Research Hospital Experience. Cancer 74:733–739, 1994.
8. Nag S, Olson T, Ruymann F, Teich S, Pieters R: High–dose-rate brachytherapy in childhood sarcomas: A local control strategy preserving bone growth and function. Medical and Pediatric Oncology 25:463–469, 1995.
9. Flamant F, Gerbaulet A, Nihoul-Fekete C, Valteau-Couanet D, Chassagne D, Lemerle J: Long-term sequelae of conservative treatment by surgery, brachytherapy, and chemotherapy for vulval and vaginal rhabdomyosarcoma in children. Journal of Clinical Oncology 8:1847–1853, 1990.
10. Gerbaulet A, Panis X, Flamant F, Chassagne D: Iridium afterloading curietherapy in the treatment of pediatric malignancies. The Institut Gustave Roussy experience. Cancer 56:1274–1279, 1985.